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THE PHARMACOLOGIC TREATMENT OF
AURICULAR FIBRILLATION

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TABLE OF CONTENTS

	Page
I. Introduction	1
II. Mechanics of Fibrillation	2
III. Treatment	3
(a) Anti-Thyroid Drugs	3
(b) Digitalis	4
(c) Quinidine	6
(d) Pronestyl	10
(e) Atabrine	12
(f) Fagarine and Chloroquine	12
IV. Summary	14
V. Conclusion	17
VI. Bibliography	

THE PHARMACOLOGIC TREATMENT OF AURICULAR FIBRILLATION

INTRODUCTION

Auricular fibrillation is the most common of all marked irregularities of the heart beat in organic heart disease. For this reason, and because of the gratifying results one achieves from its treatment, I have chosen this subject as my topic. There will be no attempt on the part of the student to discuss the etiology, diagnosis, complications, or incidence of this condition. The mechanism of auricular fibrillation will be discussed as briefly as possible only to more fully understand the rationale of its treatment.

MECHANISM OF FIBRILLATION

There are four principal theories which have been advanced to explain the physiology of this condition.

They are:

1. a rapidly beating ectopic pacemaker
2. multiple rapidly beating ectopic pacemakers
3. continuous multiple reentries initiated by a single or multiple impulses
4. a self-perpetuating mother ring caused by a single initial impulse

At present the latter of these theories is the one most widely accepted. In a review of the literature one finds convincing arguments both for and against each of the above hypotheses. However as far as treatment of auricular fibrillation is concerned, these theories are largely academic. The important thing to realize is that this condition is due to the passage of excitation waves through the non-refractory atrial syncytium in an asynchronous fashion. Thus it may be eradicated either by an over-all prolongation of the refractory phase making the chamber unresponsive to the impulse, or by increasing the speed at which these impulses travel so that they would be obliterated by arriving at regions before the absolute refractory phase was over.

TREATMENT

The treatment of atrial fibrillation has been and still is a challenging problem. There are three general types. They are: chronic, acute, and thyrotoxic auricular fibrillation. The treatment of this condition (with the exception of the latter type) consists mainly in the use of three drugs--digitalis, quinidine, and pronestyl. Atabrine, fagarine, and chloroquine have been used, but with less success.

Treatment of thyrotoxic atrial fibrillation consists of treatment of the underlying or exciting condition.

Anti-coagulant drugs are used to treat a complication of this lesion. This will be discussed below along with the drugs of choice.

Anti-thyroid Drugs

In most cases the above mentioned drugs are not so useful in the treatment of thyrotoxic atrial fibrillation. One must treat the underlying or basic lesion, and in this instance therapy consists of the anti-thyroid drugs.

For immediate action, 0.5 gm. of sodium iodide may be given. This should be followed by Lugol's solution in oral dosage along with appropriate anti-thyroid therapy.

Once the patient has been rendered euthyroid by anti-thyroid procedures, his cardiac problem is almost always resolved. If such is not the case, quinidine is indicated,

and has been found particularly useful in this instance.

Digitalis

For many years digitalis was looked upon as influencing the heart chiefly through slowing the cardiac rate, and was hence thought specific for the treatment of atrial fibrillation. Instead of being a specific anti-fibrillatory drug, digitalis has in fact just the opposite effect. It actually increases the rate of atrial fibrillation by a shortening of the refractory period thereby allowing a greater number of excitation waves to pass through the auricle.

Digitalis is administered not as a cure for this condition, but merely as a control for it. This drug is utilized primarily to control the ventricular response in presence of atrial fibrillation. It prevents this condition from going on to ventricular tachycardia and/or ventricular fibrillation, both of which have grave consequences for the patient. The drug accomplishes this control phenomena by its action in decreasing the conduction in the atrioventricular node and bundle of His. Thus a pharmacologic block is formed to protect the ventricles.

Digitalis is also used with this condition because of its beneficial effect upon cardiac function. This often alleviates the anginal and/or cerebral ischemic symptoms frequently found with atrial fibrillation.

This drug is being used less often today for the treatment of atrial fibrillation. This is because therapy is much less conservative than before. A more aggressive attack is being advocated with physicians being less selective in the patient they try to convert with the specific antifibrillatory drugs.

"Digitalis is mainly indicated in the presence of congestive cardiac failure, cardiac enlargement, in cases with rapid ventricular rates, and in cases where conversion to sinus rhythm with quinidine has failed." 20.

Classically, control is considered adequate when the heart rate is maintained around 85 beats per minute, without appreciable increase in rate with moderate exercise. As with other cardiac conditions where digitalization is indicated, dosage must be individualized. The resulting variations in cardiac response are related not only to the different characteristics of the glycosides, but also to differing responses by individual patients.

Since there is such a fine line between adequate digitalization and toxicity, one must always be alert for digitalis excess in treating this condition. The several objective clues which may warn the physician of the presence of excess digitalis are: "1. further acceleration of the ventricular rate following digitalis administration, 2. obvious independent activation of atria and ventricles (inordinately

slow, rapid, or precisely regular ventricular rates should be suspected), 3. obvious group beating (bigeminy, trigeminy, quadrageminy), 4. determination of the rate of the accelerated nodal pacemaker to be between 70-130 beats per minute." ^{11.}

Quinidine

Quinidine is the traditional drug of choice for the treatment of atrial fibrillation. "In approximately three fourths of the cases, quinidine is necessary to effect revision" ^{12.} to a normal sinus rhythm.

This drug acts as a myocardial depressant. According to Weisman ^{27.} it depresses the sinoauricular node, increases the refractory period, and decreases conduction time. It causes a prolongation of the P-R, QRS and S-T intervals.

Recently there has been a great deal of controversy over the selection of patients for conversion from atrial fibrillation to sinus rhythm. Thoughts varied from those who felt that conversion should be attempted in all instances to those who rejected conversion to normal sinus rhythm in all cases. The reasons for the latter opinion appear to be due to the belief that there is very little superiority of sinus rhythm over digitalis controlled fibrillation, and a fear of the toxic effects of quinidine.

Toxic side effects of quinidine include "a group of symptoms known as cinchonism--tinnitus aurium, blurring of vision, vertigo, tremor, and light-headedness as well as gastro-

15. 7.
intestinal distress." Reports have also linked this drug
with the development of thrombocytopenic purpura. The more
serious complications of quinidine are probably the cardiac
19.
arrhythmias it produces. These include S-A and AV blocks, and
ectopic rhythms of atrial, nodal, and ventricular origin.

Death during the course of quinide therapy is often due
to either asyctole or respiratory paralysis, neither of which
is too surprising in view of the fact that it inhibits acetyl
6.
choline which is thought to initiate the heart beat. A myo-
cardial and respiratory depressing agent is given to an
already embarrassed myocardium and a physiologically impaired
respiratory center.

A healthy respect for quinidine is of course understandable
in view of the fact that it is in reality cardiotoxic and
deaths have been reported in therapy. In view of the beneficial
results attained with proper quinidine therapy, it would appear
that the fears are largely unfounded, especially if the proper
precautions are observed.

4.
Brill urges that the following precautions be utilized
when converting a patient with quinidine. 1. Do not administer
this drug until full digitalization with a ventricular rate
of 80 or lower and maxium compensation is achieved. 2. Rule
out abnormal sensitivity to the drug with a 200 mg. test dose
on the day prior to the full dosage schedule. 3. Do not

give if the QRS is greater than 0.14 sec. 4. Before each dose, examine the patient and if hypotensive, or if there are significant signs or symptoms of toxicity, stop the drug. 5. Frequent EKG's should be taken to detect QRS widening, A-V dissociation, or complete A-V block.

The advantages of sinus rhythm were well documented by 8-10. Corday who demonstrated using catheter techniques that atrial fibrillation with a rapid ventricular rate resulted in a reduction in coronary artery flow, a lessening of cerebral blood flow, and a diminution of renal and mesenteric artery flow. In clinical observations they have further shown that relief of symptomatology (angina, dizziness) which follows a normal sinus rhythm can be correlated with improvement in blood flow to the affected parts. Patients have been reported who, before conversion, had responded poorly to digitalization, became free of symptoms after the establishment of a normal sinus rhythm.

It seems to be the consensus of opinion at this time that conversion from atrial fibrillation to a normal sinus rhythm should be attempted in all cases, except those in which a contraindication to quinidine exists. This drug is contraindicated when there is a coexistent intraventricular conduction defect or bundle branch block, or when atrial fibrillation is a result of over-digitalization. Quinidine is generally rejected

when severe congestive failure or when the heart is severely enlarged, and also when atrial fibrillation relieves precordial pain.

Quinidine is best administered via the oral or IM route. IV quinidine administration is fraught with so much hazard that administration by this avenue has largely been abandoned. In one series in which quinidine was given intravenously, the mortality rate was 10%.^{1.} Sokolow^{23.} studied the effectiveness of quinidine in the treatment of cardiac arrhythmias and correlated serum levels with effective treatment. The average serum concentration which 75-80 per cent of patients with atrial fibrillation converted was 5.4 mg. per liter. This level was achieved by administering the drug every two hours. Thus, it is widely accepted that the drug be given in divided doses^{4.} at two hour intervals. Brill recommends that quinidine sulfate U.S.P. be given 400 mg. five or six times daily for the first day. On each of the following two days, providing the arrhythmia continues and no toxic symptoms appear, the dose is increased by an increment of 200 mg. The dose may be continued for a fourth day without change in dosage. The drug is usually not continued beyond the fourth day. If conversion is not achieved, a second and even a third attempt may be attempted at intervals of several weeks. This method has met a high degree of success with very little toxicity if the previously described precautions are adhered to. Maintenance is largely a matter

of trial and error. Unfortunately, no truly effective anecdote
16. & 19.
is not available for over-dose of quinidine.

It is no longer felt that a previous history of embolism
contraindicates revision of a normal sinus rhythm through the
3.
use of quinidine. The risk of an embolic episode in the natural
course of atrial fibrillation is considered greater than it is
during conversion to sinus rhythm using quinidine. In patients
with a previous history of embolism, a course of anti-coagulant
therapy is strongly recommended as a prophylactic measure.

Pronestyl

This drug is a comparatively new addition to the physicians'
armamentarium used against atrial fibrillation compared to
13.
quinidine. It produces in man a delayed conduction rate and a
prolongation of the refractory period.

The position of pronestyl in the treatment of atrial
fibrillation appears more or less limited to the treatment of the
18.
paroxysmal variety of this condition. In one series, recent
atrial fibrillation (less than two weeks) responded to treatment
in 88% of the cases while the chronic variety (more than two
weeks) was treated successfully in only 21% of the cases. Also,
in view of the limited experience we have with procaine amide
as compared to quinidine, it would appear that the former drug
should be used when the latter cannot be tolerated. This drug is
especially efficacious in the treatment of acute atrial fibrillation

25.
since it may be administered IV with less danger than quinidine.

Contraindications and precautions to the use of pronestyl are essentially the same as those for quinidine.

Toxic side reactions have occurred involving the circulatory, gastrointestinal, and central nervous system. Ventricular extrasystoles, ventricular tachycardia, and even ventricular fibrillation may occur. Falls in BP during IV administration have occurred in a number of patients, mostly those already suffering from a degree of hypotension with ventricular tachycardia. Gastrointestinal symptoms include anorexia, nausea, and vomiting. Chills and fever and a drug rash have been reported as well.

13.
Kaydens recommends the following more or less general dosage schedule. With this drug as with other antifibrillatory agents, individualization must be made using the EKG as the main criterion of administration. When pronestyl is administered intravenously, it should not be given more than 100 mg. per minute. The dose is 200 to 1,000 mg. via this route. Orally, the drug is given in capsules of 0.25 gm., 1-2 capsules every 4-6 hours. Intramuscularly, it is recommended that it be given one gm. four times a day. Maintenance dosage should be continued for approximately four weeks after revision to normal sinus rhythm. The latter dosage schedule is again empirical.

Other Drugs

Due to the existence of the relatively safe, effective drugs

discussed (digitalis, quinidine, and pronestyl), the drugs listed below have achieved little popularity. They are mentioned mainly for the sake of completeness.

Atabrine

Atabrine acts in much the same manner as quinidine, by increasing the refractory period of the myocardium and by decreasing its excitability. This is not surprising as quinine, the classic anti-malarial drug, was the first really successful anti-fibrillatory drug used.

This drug is especially useful when quinidine has failed^{24.} and with patients who have coronary heart disease.

The dose is from 0.1 to 0.2 gms. dissolved in 10-20 ml. of normal saline, given by injection.

The use of quinacrine is limited because of its propensity to cause ventricular fibrillation. Also, there may be a yellow discoloration to the skin due to the deposition of an acridine pigment.

Fagarine and Chloroquine

These drugs have also been found to have anti-fibrillatory^{21. & 22.} properties. This property, like that of quinidine, and atabrine was found incidental to the treatment of malaria. It is felt that these drugs act by decreasing the excitability of the myocardium; however, this action has not been proven in man.

They are administered intravenously in order to be effective

21.
in the revision of sinus rhythm. However, a safe dosage
schedule has yet to be worked out. The incidence of fatal
ventricular tachycardia and fibrillation in these drugs has
22.
been too high for them to be of much use.

SUMMARY

This paper deals, as far as possible, solely with the pharmacologic treatment of atrial fibrillation. The basic mechanism of this condition is pointed out only to edify the reason for the successful action of the antifibrillatory drugs. The drugs discussed were digitalis, quinidine, and pronestyl. Atabrine, fagarine, chloroquine, and the treatment of thyrotoxic atrial fibrillation are discussed briefly.

Treatment of thyrotoxic atrial fibrillation consists of treating the basic disease process, thyrotoxicosis. For immediate action, 0.5 gm. of sodium iodide is given IV. This is followed by appropriate anti-thyroid treatment.

It was pointed out that digitalis is not a specific treatment for this condition, but merely a "control" for it. It prevents atrial fibrillation from going on to the more serious ventricular tachycardia and/or fibrillation. The drug accomplishes this control mechanism by creating a pharmacologic block in the A-V node and bundle of His. It is also utilized because of its beneficial effect on cardiac output. Classically, control is considered adequate when the ventricular rate is kept around 80 beats per minute with no appreciable increase in rate with exercise. Dosage must be individualized in order to achieve adequate control and yet avoid the pitfall of digitalis intoxication. Several objective clues to alert the physician to this hazard are listed.

Quinidine, the specific drug in the treatment of atrial fibrillation, is discussed in some detail. It can "cure" the condition, not merely "control" it. Some controversy exists today in the selection of patients for the revision of normal sinus rhythm. The old arguments that quinidine is to be feared and that sinus rhythm is little superior to digitalis controlled atrial fibrillation have largely been disproven. Experimental and clinical experiences have shown the clear cut superiority of a normal sinus rhythm. Also, if the listed precautions are observed, the fears of quinidine are largely unfounded. It would seem that unless one of the recognized contraindications exist, conversion from atrial fibrillation to normal sinus rhythm should be attempted in all instances. A dosage schedule and the rationale for the schedule are discussed along with a few words concerning embolism during revision of the physiologic heart beat.

It was pointed out that pronestyl has much the same mode of action as does quinidine. It is best used when the patient cannot take quinidine, and when the arrhythmia is acute in nature. Contraindications and precautions for this drug are much the same as those for quinidine. An added value is that pronestyl can be given IV much safer than may quinidine. Also, a fairly effective anecdote is available. A rough dosage schedule and its untoward effects are discussed.

The other drugs used in the treatment of this condition--

atabrine, fagarine, and chloroquine were discovered incidental to malarial therapy. They have met little popularity because of their tendency to cause ventricular tachycardia and/ or fibrillation.

CONCLUSION

1. Thyrotoxic auricular fibrillation is best treated by attacking the basic disease process with anti-thyroid therapy.
2. Digitalis is indicated to "control" auricular fibrillation and to prepare the patient for revision to normal sinus rhythm.
3. Revision to normal sinus rhythm should be attempted in all incidences unless there is a contraindication to the use of quinidine (and pronestyl).
4. Pronestyl is indicated when quinidine cannot be tolerated by the patient, and in the revision of acute fibrillation.
5. Fagarine, chloroquine, and atabrine have met with little popularity in the treatment of auricular fibrillation because of their tendency to cause ventricular tachycardia and/or fibrillation.

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